PTO 1390 Page 1 of 1 | US Dept. of Commerce Pat. & Trademark Office | Attorney's Docket No. 21965

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 USC 371

US. Application No. (if known) 09/890029

INTERNATIONAL APP. NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/HU00/00009	**28 January 2000**	**1 February 1999**

TITLE OF INVENTION

PHARMACEUTICAL COMBINATION OF PROGESTERONE AND FOLIC ACID

APPLICANT(S) FOR DO/EO/US

Gabor BOGYE

Applicant herewith submits to the United States Designated/Elected Office (DO/EU/US) the following .

1. ■ This is a **FIRST** submission of items concerning a filing under 35 USC 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 USC 371.
3. ☐ This is an express request to begin national examination procedures (35 USC 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 USC 317(b) and PCT Articles 22 and 39(1).
4. ■ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ■ A copy of the International Application as filed (35 USC 371(c)(2)). (IN ENGLISH)
   a. ■ is transmitted herewith (required only if not transmitted by the International Bureau.
   b. ☐ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Patent Office.
6. ☐ A translation of the International application into English.
7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 USC 371(c)(3)).
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau.
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 USC 371(c)(3).
9. ■ An oath or declaration of the inventor(s) (35 USC 371(c)(4).
10. ■ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 USC 371(c)(5)).

Items 11. to 16. below concern documents or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An Assignment for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☐ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ■ Other items of information.

US Application no (if known)	International Application no.	Attorney's Docket No.
09/890029	PCT/HU00/00009	21965

JC17 Rec'd PCT/PTO 24 JUL 2001

17. The following fees are submitted:	CALCULATIONS PTO USE ONLY	
Basic National Fee (37 CFR 1.492(a)(1)-(5)):		
Search report has been prepared by the EPO or JP $860.00		
Int'l prel. exam. fee paid to USPTO (37 CFR 1.482) $690.00		
No int'l prel. exam. fee paid to USPTO (37 CFR 1.482) but int'l search fee paid to USPTO (37 CFR 1.445(a)(2) $710.00		
Neither int'l prel. exam fee (37 CFR 1.482) nor int'l search fee (37 CFR 1.455(a)(2)) paid to USPTO $1000.00		
Intl. prel. exam. fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Art. 33(2-4) $100.00	**$1,000**	
ENTER APPROPRIATE BASIC FEE AMOUNT		
Surcharge of $130.00 for furnishing oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).		

CLAIMS	NO. FILED	NO. EXTRA	RATE		
Total claims	**8**	**0**	$18	**$0**	
Ind. claims	**0**	**0**	**$80**	**$0**	
MULTIPLE DEP. CLAIM(S) (if applicable) **(see prel. amt.)**			**270**		
TOTAL OF ABOVE CALCULATIONS				**$1,000**	
Reduction of ½ for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (37 CFR 1.2, 1.27, 1.28)				**$500**	
SUBTOTAL				**$500**	
Processing fee of $130.00 for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)).					
TOTAL NATIONAL FEE				**$500**	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The Assignment may be accompanied by an appropriate PTO-1595 cover sheet (37 CFR 3.28, 3.39)					
TOTAL FEES ENCLOSED					
				Amt to be refunded	
				Amt to be charged	

a. ☐ A check in the amount of $ to cover the above fees is enclosed
b. ☐ Please charge my deposit account 18-2025 $ to cover the above fees. A copy of this sheet is enclosed.
c. ■ Please charge the amount due to the credit card identified in the attached PTO-2038.
d. ■ The commissioner is authorized to charge any additional fees which may be required or credit any overpayment to deposit account 18-2025. A copy of this sheet is enclosed
e. A PTO-2038 in the amount of $ to cover recordal of the Assignment is enclosed

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

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PHARMACEUTICAL COMBINATION OF PROGESTERONE AND FOLIC ACID

The present invention relates to pharmaceutical composition(s) comprising gestogen type steroid hormone(s) and compound(s) lowering in human plasma the level of homocysteine, capable of lowering the risk of thromboembolic side effects of gestogen type compositions.

It has been known that the most important side effect of the use of some compositions containing steroid hormones, such as gestogen, is the increased occurrence of thromboembolic diseases. These side effects may occur upon the administration of any pharmaceutical composition comprising gestogen type hormone and they are often lethal.

This problem has been solved so far by two methods:

a) Patients, in case of which the probability of the occurrence of thromboembolic side effects is rather high (adipose, smokers, patients of the age above 35, patients whose anamnesis already showed thromboembolic disease), were excluded from this hormone therapy.

b) On the basis of the positive correlation of the occurrence of the thromboembolic complications and the dose of the used hormone by decreasing the hormone content of the pharmaceutical compositions the occurrence of the thromboembolic complications could be reduced.

These known methods show numerous disadvantages:
The patients excluded from the hormone therapy on the basis of the absolute and relative contraindications, could not obtain an otherwise necessary treatment.

By reducing the hormone content of the given pharmaceutical composition, not only the occurrence of the side effects is reduced, but the extent and safety of the effect to be achieved, too.

A further disadvantage of this latter known method is that although the risk of the occurrence of the side effects is reduced, the potentially lethal side effects cannot be entirely eliminated.

There is a continuous need for such novel compositions, the use of which results in a lower risk of thromboembolic diseases than with the known compositions, while maintaining the original activity of the hormone(s).

On the basis of recent research it has become known, that the increase of the homocysteine content in the human plasma is an independent risk factor of arterial and venal thrombosis and embolism. We refer to the latest studies summarising this problem: *(Welch GN, Loscalzo J. Homocysteine and atherothrombosis. N Engl J Med 1998, 338:1042-50.; den Heijer M, Kostor T, Blom HJ, et al. Hyperhomocysteinemia as a risk factor for deep-vein thrombosis. N Engl J Med 1996, 334:759-62.; Graham IM, Daly IE, Refsum H, et al. Plasma homocysteine as a risk factor for vascular disease. JAMA 1997, 277:1775-81.).*

In EP 0347864 A2 (Strydom, Andries Johannes Cornelus: Anti-atherogenic agents) the authors disclose that atherosclerosis can be reduced by using some pharmaceutical compositions reducing the homocysteine content of the plasma and/or arterial wall.

As opposed to the contents of said patent specification, we have recognised that the increased homocysteine content of the plasma itself induces susceptibility to thromboembolism before leading to atherosclerosis. Therefore the aim of our invention was not only to

prevent or reduce atherosclerosis by reducing the homocysteine content in the plasma, but to achieve the prevention of thromboembolism occurring independently of atherosclerosis.

Some compounds (folic acid, vitamin B_6, vitamin B_{12}, betaine, choline, acetyl cysteine) reduce the homocysteine content of the plasma in case of certain types of hyperhomocysteinaemia (not all types). (Welch GN, Loscalzo J. Homocysteine and atherothrombosis. N Engl J Med 1998, 338:1042-50.; Refsum H, Ueland PM. Clinical significance of pharmacological modulation of homocysteine metabolism. TiPS 1990, 11:411-6.)

In case of some of these vitamins B (folic acid, vitamins B_6 and B_{12}), it can be considered as proven that they reduce the occurrence of thromboembolic complications not induced by medicines.

(Graham IM, Daly IE, Refsum H, et al. Plasma homocysteine as a risk factor for vascular disease. JAMA 1997, 277:1775-81.; Herbert V, Bigaouette J. Call for endorsement of a petition to the Food and Drug Administration to always add vitamin B12 to any folate fortification or supplement. Am J Clin Nutr 1997, 65:572-3.).

In case of steroid hormones containing ostrogen, it has been already suggested that these hormones tend to make susceptible to thromboembolism through the increase of the homocysteine content of the plasma, but this hypothesis could not be proved by tests carried out so far. (*Brattstrom L, Israelsson B, Olsson A, Andersson A, Hultberg B. Plasma homocysteine in women on oral oestrogen-containing contraceptives and in men with oestrogen-treated prostatic carcinoma. Scand J Clin Invest 1992, 52:283-7.).*

We have now surprisingly found that the occurrence of thromboembolic diseases which can be correlated with the administration of pharmaceutical compositions containing gestogen type steroid hormone, is greatly due to the plasma homocysteine level increasing activity of the gestogen hormones. We have further recognised that this increase of the plasma homocysteine level

caused by gestogen hormones can efficiently be reduced or prevented by known homocysteine level reducing agents, e.g. folic acid, vitamin B_6, vitamin B_{12}, betaine, choline, acetyl cysteine and metabolic precursors, analogues and/or derivatives thereof.

According to the invention there is provided a solution to the above-mentioned aim, we can reduce the increased homocysteine level or prevent the increase thereof induced by certain gestogen type hormones independently from atherosclerosis. This decrease or prevention can be achieved by such homocysteine level reducing agents, which have not been used for this purpose so far.

The present invention provides pharmaceutical composition(s), which reduce(s) the risk of the thromboembolic side effects of gestogen hormone containing medicines.

The pharmaceutical composition(s) according to the invention comprise an efficient amount of gestogen type steroid hormone(s), metabolic precursor(s), analogue(s) and /or derivative(s) thereof, and an efficient amount of plasma homocysteine level reducing compound(s) e.g. folic acid, vitamin B_6, vitamin B_{12}, betaine, choline, acetyl cysteine and metabolic precursors, analogues and/or derivatives thereof.

It is a favourable feature of the pharmaceutical compositions according to the invention that the hormone component(s) thereof is (are) suitable for contraception, hormone substituting therapy, antiinflammation, promoting in vitro fertilisation, dermatological therapy and/or cosmetological treatment and the compositions may be used for these purposes.

The hormone component and the homocysteine level reducing component may be administered separately, but it is preferred to administer the active components in the form of one composition. No such compositions are available on the market at the present.

On the basis of the above recognition we have come to the following unexpected results

- the pharmaceutical compositions containing gestogen type steroid hormones increase the homocysteine concentration of the plasma, meaning the increase of the risk of thromboembolic diseases
- the increased plasma homocysteine level due to a medicine containing gestogen type hormone can especially efficiently be reduced by folic acid and vitamin B_6. We note that on the basis of data having been available for us before our investigations, one could not come to the conclusion that vitamins B would be efficient against hyperhomocysteinaemia induced by medicines comprising gestogen type hormones, as folic acid and vitamin B_6 are not efficient in all types of hyperhomocysteinaemia. *(Hong SY, Yang DH, Chang SK: Plasma homocysteine, vitamin B_6, vitamin B_{12} and folic acid in end-stage renal disease during low-dose supplementation with folic acid. Am J Nephrol 1998, 18:367-372.)*.
- In hyperhomocysteinaemia induced by medicines comprising gestogen type hormones the folic acid and vitamin B_6 therapy results in a much more intensive plasma homocysteine level reduction than it could have been expected on the basis of the prior art. According to the prior art in case of folic acid therapy against folic acid deficiency, the plasma homocysteine concentration is diminished on an average by 45 to 50% and in case of hyperhomocysteinaemia of genetic origin on an average by 20 to 25 %. *(Guttormsen AB, Schneede J, Ueland PM, Refsum H. Kinetics of total plasma homocysteine in subject with hyperhomocysteinemia due to folate or cobalamin deficiency. Am J Clin Nutr 1996, 63:194-202.)*.

The advantage of the pharmaceutical composition(s) according to the invention and of the use thereof against compositions containing only hormone is the smaller risk of thromboembolic side effects. The use of gestogen type hormones becomes safer by the pharmaceutical composition(s) according to the invention and one can expect that for patient groups (smokers, patients above the age of 35, patients

suffering from overweight, in case of anamnestic data etc.), who were excluded from the use of compositions containing solely hormone, said pharmaceutical composition(s) can be prescribed. A further advantage is that both the hormone(s) and the compounds reducing the plasma homocysteinaemia concentration will be finished in one dosage unit (tablets, capsules, ampoules, powder, solution, granules, syrup etc.) ensuring thereby the simultaneous application of the hormone active ingredient and the „antidote" acting against the most important side effect of the hormone, i.e. the plasma homocysteine reducing agent. The hormone component(s) and the plasma homocysteine level reducing compound(s) may be applied in separate dosage units as well, as according to our test results both in case of simultaneous and separate administration, hyperhomocysteinaemia induced by gestogen hormones may be reduced or prevented.

The invention accordingly further provides a method for treating patients, taking medicines containing gestogen type hormone(s), by the administration of a pharmaceutical composition according to the invention at an effective dosage or by the administration of plasma homocysteine content reducing agents, selected from folic acid, vitamin B_6, vitamin B_{12}, betaine, choline, acetyl cysteine and metabolic precursors, analogues and/or derivatives thereof in addition to the gestogen containing pharmaceutical composition.

The effective dosage is generally in the range of from 100 microgram to 9 gram per day of plasma homocysteine content reducing agents (for example it ranges from 0.5 mg to 5 mg per day of folic acid, from 10 mg to 300 mg of vitamin B_6, from 300 microgram per day to 5 mg per day of vitamin B_{12}, from 0.5 g to 9 g per day of betaine and from 100 mg to 1 g per day of acetyl cysteine).

The effective dosage of gestogen components is generally in the range of 0.05-5 mg per day.

We illustrate our invention by the following non-limiting examples:

Example a)

47 healthy women of middle age were involved in the test, who were divided in two groups on the basis of taking or not taking contraceptives, and then their fasting plasma homocysteine concentration was measured by HPLC method. The average homocysteine content of the women obtaining entirely or partially gestogen containing contraceptive therapy (daily 1) 0.15 mg of levonorgestrelum and 0.03 mg of aethinyloestradiolum, or 2) 0.25 mg of levonorgestrelum and 0.05 mg of aethinyloestradiolum, or 3) 0.15 mg of desogestrelum and 0.03 mg of aethinyloestradiolum, or 4) 0.075 mg of gestodenum and 0.03 mg of aethinyloestradiolum, or 5) 0.25 mg of norgestinatum and 0.035 mg of aethinyloestradiolum, or 6) 0.5 mg of aethynodiolum diaceticum) was significantly higher than that of the control group.

Example b)

32 healthy women of middle age were involved in the test, who were taking oral contraceptive of gestagen content (daily 1) 0.15 mg of levonorgestrelum and 0.03 mg of aethinyloestradiolum, or 2) 0.25 mg of levonorgestrelum and 0.05 mg of aethinyloestradiolum, or 3) 0.15 mg of desogestrelum and 0.03 mg of aethinyloestradiolum, or 4) 0.075 mg of gestodenum and 0.03 mg of aethinyloestradiolum, or 5) 0.25 mg of norgestinatum and 0.035 mg of aethinyloestradiolum, or 6) 0.5 mg of aethynodiolum diaceticum). The fasting plasma homocysteine content was measured by HPLC method. We have found that the extent of increase of the plasma homocysteine content was in correlation with the daily dosage of gestogen, or we also noticed an increase of the plasma homocysteine content, when exclusively gestogen containing composition was administered to the patients. It is apparent that gestogens are responsible for the increase of the homocysteine concentration.

Example c)

We have examined 31 healthy women of middle age who obtained next to a gestogen containing contraceptive (daily 1) 0.15 mg of levonorgestrelum and 0.03 mg of aethinyloestradiolum, or 2) 0.25 mg of levonorgestrelum and 0.05 mg of aethinyloestradiolum, or 3) 0.15 mg of desogestrelum and 0.03 mg of aethinyloestradiolum, or 4) 0.075 mg of gestodenum and 0.03 mg of aethinyloestradiolum, or 5) 0.25 mg of norgestinatum and 0.035 mg of aethinyloestradiolum, or 6) 0.5 mg of aethynodiolum diaceticum) 1 or 3 mg/die of folic acid or 20 mg/die of vitamin B_6 and when the fasting plasma homocysteine concentration was measured by HPLC method, a significant ($p<0.05$) reduction (on an average by 69%) was observed. Some participants (n=14) obtained separately vitamin tablets next to the contraceptive tablets, and in other cases (n=17) the contraceptive and the folic acid or vitamin B_6 were ground to a powder, admixed and filled to cachet or capsule and the mixture thus obtained was administered. As to the plasma homocysteine concentration no difference could be shown between the two methods of administration (in separate tablets or one single formulation). During the observation period no undesired pregnancy or thromboembolic complication occurred.

Example d)

In case of 6 women during a gestogen hormone therapy, which was used in the in vitro fertilisation program (the dosage of 600 mg/die progesterone was gradually reduced during 12 weeks), the change of fasting plasma homocysteine concentration was measured by HPLC method. The result was that the plasma homocysteine concentration changed proportionately with the dosage of gestogen.

Example e)

During taking gestogen containing hormone (600 mg/die of progesterone) the fasting plasma homocysteine concentration was

measured, and the therapy was then supplemented with 1 mg/die and 3 mg/die of folic acid or 20 mg/die of vitamin B_6 by placing the hormone in the form of micronised progesterone and the vitamin B in the form of folic acid or vitamin B_6 into a capsule or cachet, which was administered. The plasma homocysteine concentration was reduced on an average by 65%.

The pharmaceutical compositions according to the invention may be prepared by methods known per se. Depending on the route of administration one can prepare tablets, vaginal tablets, capsules, granules, cachets, syrup, solution, dragées, suppositories, ampoules etc.

We can accordingly add the conventionally used solid or liquid carriers to the active ingredients. As solid carrier one may use aroma substances, lubricating agents, solubilisers, suspending agents, gliding agents, disintegrating agents, tabletting or capsulating agents, such as magnesium stearate, talc, methyl cellulose, gelatine, sodium carboxymethyl cellulose, polyvinyl pyrrolidone, lactose etc.

As liquid carriers one may use e.g. buffers, preservatives, agents controlling viscosity or osmotic pressure, emulsifiers, solubilisers, sweetening agents, such as water, cellulose derivatives, alcohols, oils or oil esters etc.

Hereinbelow we give the short description of the preparation of compositions containing the hormone and the compound reducing the plasma homocysteine concentration:

Example A: Tablets containing 1) 0.15 mg of levonorgestrelum and 0.03 mg of aethinyloestradiolum, or 2) 0.25 mg of levonorgestrelum and 0.05 mg of aethinyloestradiolum, or 3) 0.15 mg of desogestrelum and 0.03 mg of aethinyloestradiolum, or 4) 0.075 mg of gestodenum and 0.03 mg of aethinyloestradiolum, or 5) 0.25 mg of norgestinatum and 0.035 mg of aethinyloestradiolum, or 6) 0.5 mg of aethynodiolum

diaceticum were ground to powder, whereafter tablets containing 1 mg or 3 mg folic acid or 20 mg of vitamin B_6 were added in the form of powder. The mixture was filled into cachets or hard gelatine capsules.

Example B: Soft gelatine capsules containing 500 mg of micronised progesterone were opened, and tablets containing 3 mg of folic acid or 20 mg of vitamin B_6 were ground to powder. The oil content of the progesterone tablets was absorbed by the powder of the vitamin tablets and this was filled into hard gelatine capsules, sealed or packed into cachets.

Claims

1. Use of a plasma homocysteine content reducing agent in compositions comprising a gestogen type hormone for the reduction of thromboembolic side effect risk induced by the hormone.

2. Use as claimed in claim 1, comprising using as plasma homocysteine content reducing agent an efficient amount of folic acid, vitamin B_6, vitamin B_{12}, betaine, choline, acetyl cysteine, metabolic precursors, analogues and/or derivatives thereof.

3. Use as claimed in claim 1, comprising using as plasma homocysteine content reducing agent an efficient amount of folic acid.

4. Use as claimed in claim 1, comprising using as plasma homocysteine content reducing agent an efficient amount of vitamin B_6.

5. Use as claimed in claim 1, comprising as gestogen type hormone an efficient amount of progesterone type hormone(s), metabolic precursor(s), analogue(s) and/or derivative(s) thereof.

6. Use as claimed in claim 1, comprising using the plasma homocysteine content reducing agent simultaneously, previously or subsequently with gestogen type hormone.

7. Method of treatment of patients taking gestogen type hormone compositons, which comprises administration of an effective dosage of a composition as claimed in claim 1.

8. Method of treatment of patients taking gestogen type hormone compositons, which comprises administration of an effective amount of plasma homocysteine content reducing agents, selected from folic acid, vitamin B_6, vitamin B_{12}, betaine, choline, acetyl cysteine, metabolic precursors, analogues and/or derivatives thereof.

21965

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that: My residence, post-office address, and citizenship are as stated below next to my name,
I believe that I am the original, first, and sole inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled

PHARMACEUTICAL COMBINATION OF PROGESTERONE AND FOLIC ACID

the specification of which was filed on **28 January 2000** as PCT application **PCT/HU00/00009.**
I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims.
I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.
I hereby claim foreign priority benefits under 35 USC 119 of any foreign applications for patent or inventor's certificate listed below and have also identified below any foreign applications for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Applications

Country	Number	Filing Date	Priority claimed
HU	**P9900213**	**1 February 1999**	**Yes**

I hereby claim the benefit under 35 USC 120 of the United States Application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States Application(s) in the manner provided by the first paragraph of 35 USC 112, I acknowledge the duty to disclose material information as defined in 37 CFR 1.56 which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Serial Number	Filing Date	Status
PCT/HU00/00009	**28 January 2000**	**Pending**

I hereby appoint as attorneys to prosecute this application and to transact all business connected therewith: **Herbert Dubno**, Reg. 19,752; **Jonathan Myers**, Reg. 26,963; **Andrew Wilford**, Reg. 26,597 and each of them individually.
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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 USC 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole inventor: ***Gabor BOGYE***

Inventor's signature G. Bogye Date: 11.07.2001

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